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# LETTERS TO THE EDITOR

## Heart Disease in Diabetes—Resist the Beginnings

The study by Fang et al. (1), together with the accompanying editorial by Picano (2), draws attention to early functional changes of the heart in diabetes. It is tempting to take the story one step further: to consider the consequences of changes in energy substrate supply to the heart. Diabetes is as much a disorder of dysregulated fatty acid metabolism as it is a disorder of dysregulated glucose metabolism (3), and, in the blood of diabetic patients, fatty acid levels are elevated along with glucose levels. We have found substantial changes in the metabolic gene expression profile of hearts from diabetic animals before the onset of functional abnormalities (4,5). This is one end of the spectrum. At the other end of the spectrum, the transcriptional profile of diabetic patients with heart failure reveals a severe downregulation of the myocyte enhancer factor-2 (MEF2C) and its target genes (6) contributing to more severe contractile dysfunction. We proposed that metabolic remodeling in diabetes precedes, causes, and sustains the functional and structural remodeling of the heart (7,8). Consequently, early detection and correction of the metabolic abnormalities should also prevent the heart's functional decline later on. When used early enough, new pharmacological agents directed at metabolic targets may prevent a significant amount of cardiovascular disease (9). The Romans used to have a term for this: *Principiis obsta*—"Resist the beginnings."

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## REPLY

I greatly appreciate the thoughtful comment of Drs. Taegtmeyer and Razeghi. In my editorial to the study by Fang et al. (1), I described an "echocardiographic cascade" in the natural history of diabetic cardiomyopathy, with subtle, preclinical, possibly reversible changes in inotropic reserve, coronary flow-reserve, and ultrasonic tissue structure preceding more advanced, profound, and less, if at all, reversible changes in resting regional or global systolic function (2). No doubt that echocardiographic signs—however early—are only the consequences of the altered upstream metabolic and/or genetic condition. I proposed metabolic changes (with nonenzymatic glycation), according to what seemed to me (a metabolically and simple minded clinical cardiologist, I must admit) the most likely and proven explanation to date. There is little surprise to learn that knowledgeable experts propose a more sophisticated and elegant explanation: a genetically regulated disturbance in fatty acid metabolism that is present in both early and in more advanced phases of diabetic cardiomyopathy.

I do not know whether this is the only truth, but most likely it is part of it. In diabetic cardiomyopathy, disturbances in glucose metabolism coexist with alterations in fatty acid metabolism. Further upstream, there could be oxidative somatic DNA damage, which may co-generate and amplify the onset of clinical complications (3). Each of these components (genetic, metabolic, inflammatory, etc.) is part of a multifaceted and—at least for the clinician—still elusive pathogenetic entity. The quest for the holy grail of the metabolic source of diabetic cardiomyopathy cascade is still ongoing. Only by drying the (metabolic and/or genetic) source can we hope to halt the cardiomyopathy cascade that eventually leads the diabetic patient to heart failure and cardiac death. However, we are far from achieving this goal. The Romans used to have a term for this: *Acta est fabula:* "The game has just started."

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